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***Via Hand Delivery - Date Stamped Return Receipt Requested***

Division of Dockets Management
U.S. Food and Drug Administration
U.S. Department of Health and Human Services
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD 20852

**CITIZEN PETITION**

The undersigned, on behalf of Breckenridge Pharmaceutical, Inc. ("Breckenridge"), submits this petition in accordance with §§ 201 (p), 501, 502, and 505 of the Federal Food, Drug and Cosmetic Act ("FDC Act")[1], as well as 21 C.F.R. §§ 10.20, 10.30, 320.32, and 320.33, requesting that the Commissioner of Food and Drugs:

> *Establish criteria, analogous to the criteria for marketing Category I drug products under the Over-the-Counter ("OTC") Drug Review, that will permit state boards of pharmacy, pharmacy and therapeutics ("P&T") committees, private insurers, and information services to determine the substitutability of prescription hyoscyamine drug products under state pharmacy law in order to reduce their drug costs with the input of FDA. De facto criteria exist, and these criteria are necessary to prevent the misuse of FDA's Approved Drug Products with Therapeutic Evaluations (commonly referred to as the "Orange Book"). These*

[1] 21 U.S.C. §§ 301 et seq. (hereinafter, all citations will be to the FDC Act).

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*drugs are marketed under the rubric of Drug Efficacy Study Implementation ("DESI") II, grandfather, Paragraph XIV (or Generally Recognized as Safe and Effective ("GRAS/E")) and subject to regulation under FDA's draft guidance on Marketed Unapproved Drugs-Compliance Policy Guide, which supersedes Section 440.100, Marketed New Drugs Without Approved NDAs or ANDAs (Compliance Policy Guide ("CPG") 7132c.02).*

The Food and Drug Administration ("FDA" or the "Agency") has established equivalence standards for prescription drug products with approved applications under the FDC Act, as well as drug products that are GRAS/E for OTC use. The Agency's almost half century of extremely limited regulatory action against drugs falling under the above cited rubric has created a *de facto* category of GRAS/E drug products. This justified restraint has unfortunately permitted some companies to make broad, unsubstantiated assertions about the availability of market exclusivity and non-substitutability under the FDC Act and the Orange Book for their hyoscyamine drug products. FDA's inaction has led a federal district court to potentially usurp FDA's primary jurisdiction in at least five areas and establish standards that are inconsistent among the states and inconsistent with FDA's standards, creating novel and inappropriate intellectual property standards.

The *de facto* GRAS/E equivalence criteria for hyoscyamine prescription drug products that should be formally acknowledged are analogous to the criteria for OTC Category I drug products and therapeutic equivalence criteria for drug products that have contemporarily approved New Drug Applications ("NDAs") and Abbreviated New Drug Applications ("ANDAs") since September 1984. The criteria are as follows: (1) there is a long history of safe active pharmaceutical ingredient ("API") usage as a prescription drug product, *i.e.*, use for a material time or to a material extent; (2) the products are marketed in the same basic dosage form, *i.e.*, pharmaceutical equivalence; (3) the labeling among the products is similar, but not necessarily identical, *i.e.*, adequate labeling; (4) the products comport with the applicable compendial criteria; and they are manufactured in compliance with current good manufacturing practices ("cGMPs"), *i.e.*, equivalence.

The above sought Agency action which should adopt the *de facto* criteria, is necessary under the FDC Act for FDA to maintain its primary jurisdiction to determine the following: (1) the legal status of these prescription drug hyoscyamine products; (2) the legal standards for making and asserting market exclusivity; (3) the scientific standards for marketing these products; (4) the labeling and advertising of these products; and (5) the scientific standards for recommending or permitting the substitution of these products.

## STATEMENT OF THE GROUNDS

## I. HISTORICAL BACKGROUND

### A. Drug Amendments of 1962 and the DESI Review

#### 1. Overview of the DESI Program

The 1962 Kefauver-Harris Drug Amendments ("1962 Amendments" or "Drug Amendments of 1962")[2] were significant to new drug approvals in that, for the first time, FDA required drug sponsors not only to demonstrate the safety of new drugs but also to prove their effectiveness. The 1962 Amendments also applied retroactively, so that drugs that were already approved for safety were required to go through an additional review process to establish their effectiveness.[3] Under a government contract, the National Academy of Sciences ("NAS") and the National Research Council ("NRC") were charged with reviewing the effectiveness of all drugs that had received FDA approval from 1938 until 1962.[4]

During this time period, FDA issued innumerable "not new drug" letters to companies seeking to market identical, similar, or related ("ISR") drug products containing the same active ingredient as the one marketed under an NDA that became effective on safety grounds. These letters resulted in hundreds of thousands of such drug products entering the market without prior

[2] Pub. L. No. 87-781 (Oct. 10, 1962).
[3] *Id.* at Section 107.
[4] 31 Fed. Reg. 9426 (July 9, 1966).

FDA review. The requirement that the effectiveness standard of adequate and well-controlled investigations be applied to all drugs approved between 1938 and 1962 formed the basis for the DESI review, and the review process was performed on the basis of the API. The findings were applied to the API and all ISR drug products.[5] The DESI Review program was initiated in the mid-1960's and reached its zenith in the 1970's. The program has never been completed and has become an extremely low regulatory priority for FDA.

As a result, guidance CPG 7132c.02[6] sets forth FDA's current policy for reviewing products that are the subject of safety-only NDAs, certain unapproved new drugs, and their "me-too" copies, *i.e.*, the ISR drug products. The prescription drugs governed by CPG 7132c.02 fall essentially into two general groups. The first group includes APIs that were marketed between 1938 and 1962 and were the subject of safety-only NDAs, or me-too copies of those NDA drugs (the DESI drugs). The second group consists of drugs, regardless of when they were marketed, that were never the subject of an NDA and includes: (1) drugs marketed prior to 1984 that were never the subject of an NDA; and (2) copies of those drugs, regardless of when they were marketed. These products are subject to the so-called "DESI II" (or "Prescription Drug Wrap-Up") program, which will begin upon completion of the DESI I program.[7]

In theory, all of these drugs are currently under review under the DESI programs with the purpose of confirming their effectiveness. As a practical matter, however, no current action or program is ongoing. The drugs theoretically under review in both DESI I and DESI II have been merged into one group and are listed in a document referred to as the "Weiss list", which was provided to Congressman Weiss (D-NY) in response to a request in 1984 for a full list of all drugs that were marketed without full contemporary NDA approvals.[8] A drug appearing on the Weiss list that is not the subject of a final DESI I notice or FDA enforcement action may be

[5] 21 C.F.R. § 310.6. For a lucid description of this process, *see* 40 Fed. Red. 26142 (June 20, 1975).
[6] "Marketed New Drugs Without Approved NDAs or ANDAs (CPG 7132c.02)", Compliance Policy Guides Manual, Sec. 440.100 (March, 1995).
[7] In total, the DESI program evaluated over 3,000 separate products and over 16,000 therapeutic claims.
[8] Compliance Report for DESI-2, DRLS-DESI-2 1000 (printout dated Sept. 3, 1987).

marketed lawfully.[9] Under CPG 7132c.02, the Agency has stated that, pending the review for a particular DESI drug or its "me-too" copies, it will generally refrain from taking enforcement action against an unapproved new drug or an ISR product that was marketed as of November 13, 1984 and for which FDA has not yet made a decision as to its marketing status. By regulation § 310.6, FDA applied the DESI findings of effectiveness to all drug products that are ISR to those drug products that have been the subject of DESI notices[10] *i.e.*, it regulated the area on an API basis; and FDA has enforced this policy of regulating on the basis of the API for the drugs on the Weiss list when necessary. Hyoscyamine drug products are on that list and subject to regulation on an API basis.[11]

### 2. Paragraph XIV Status

*American Public Health Association v. Veneman*[12] created the "Paragraph XIV" class of drugs as a subset of DESI drugs. These drugs were permitted by FDA to remain in the marketplace pending additional testing to establish their effectiveness.[13] Paragraph XIV of the court order in *American Public Health Association v. Veneman* gave the Agency the discretion, regarding the continued marketing of drugs that were less than effective and part of the DESI program. The exemption was created to give companies more time to design and execute additional studies to ascertain effectiveness for the products that meet a "compelling medical need."[14] Again, this category of drugs has been regulated on an API basis. Hyoscyamine prescription drug products are covered by Paragraph XIV.

### 3. FDA's Authority to Regulate Prescription Drug Advertising

The Drug Amendments of 1962 also transferred the authority to regulate the advertising of prescription drug products from the Federal Trade Commission ("FTC") to FDA.[15] Specifically, the FDC Act was amended to provide that no prescription drug advertisement issued after the implementing regulations became effective would be subject to the FTC Act; to

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[9] "Marketed New Drugs Without Approved NDAs or ANDAs (CPG 7132c.02)", Compliance Policy Guide, Sec. 440.100 (March, 1995).
[10] 21 C.F.R. § 310.6.
[11] Compliance Report for DESI-2 (printout dated Sept. 3, 1987).
[12] *American Pub. Health Ass'n v. Veneman*, 349 F. Supp. 1911 (D.D.C. 1972).
[13] 46 Fed. Reg. 48549, 48551 (Oct. 1, 1981); *North Am.Pharmacal v. HEW*, 491 F.2d 546 (8th Cir. 1973).
[14] *Id.* (citing *American Pub. Health Ass'n v. Veneman*); 56 Fed. Reg. 59288 (Nov. 25, 1991).

the extent those matters are covered by the FDA regulations.[16] Further, under a Memorandum of Understanding ("MOU") between FDA and FTC, FDA has since regulated all matters involving the labeling of drugs and the truth or falsity of prescription drug advertising, whereas FTC regulates the truth or falsity of OTC drug advertising.[17]

The FDA regulations governing prescription drug advertising are comprehensive. They include specific provisions regarding the presentation of advertising materials as well as the content and dissemination.[18] The comprehensive regulations in 21 C.F.R. Part 202 cover everything from nomenclature to name placement,[19] prominence, scope and substance of information in the ads,[20] qualification for the truthfulness of the statement, explanation of the fair balance requirement, and criteria for determining if the advertising is false and misleading.[21] The Agency also requires submission of the advertising and, in certain situations, pre-clearance.[22] Direct-to-Consumer advertising is also covered.[23]

### B. OTC Drug Review

Four hundred twenty (420) of the five thousand (5,000) NDAs approved between 1938 and 1962 were for OTC drug products. Although subject to the DESI Review program in May 1972, FDA decided to develop a comprehensive, separate program to regulate the almost 400,000 OTC products in the U.S. market through an administrative review ("the OTC Drug Review").[24]

Prior to 1972, these OTC products were marketed under a risk that FDA could seize any product it determined was not GRAS/E. Without prior notice, FDA could assert that an OTC

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[15] Pub.L.No. 87-781, Sec. 131 (Oct. 10, 1962); Memorandum of Understanding with Federal Trade Commission Concerning Exchange of Information (Oct. 1., 1980).
[16] FDC Act § 502(n), as amended.
[17] MOU with Federal Trade Commission Concerning Exchange of Information, FDA-225-71-8003 (Oct. 1, 1980).
[18] *See generally* 21 C.F.R. Part 202.
[19] *See* 21 C.F.R. § 202.1(b).
[20] *See* 21 C.F.R. § 202.1(e).
[21] *See* 21 C.F.R. § 202.1(e)(7).
[22] *See* 21 C.F.R. § 202.1(j).
[23] Guidance for Industry, Consumer Directed Broadcast Advertisements, DDMAC (Aug. 1999).
[24] *See* 21 C.F.R. § 330.10; 37 Fed. Reg. 85 (Jan. 5, 1972), 37 Fed. Reg. 9464 (May 11, 1972).

drug product was not GRAS/E and thus was a new drug without an approved NDA. The drug product could be seized as a violative drug, and the manufacturer was also subject to legal action for introducing such a violative product in interstate commerce.[25] FDA regulatory action was seldom initiated against such products unless safety issues attributable to the API arose. When the OTC Review process commenced, its purpose was to establish clear legal and scientific rules by which FDA was going to regulate all OTC products.[26] FDA initiated this transparent multi-step administrative process, which was based on the DESI Review process, so that the public and industry would know which APIs were GRAS/E.[27] For products containing such drugs, no additional testing or FDA approval was required for marketing.

Under the OTC monograph system, FDA sets forth permissible "conditions for marketing" for categories of drugs, *e.g.*, analgesics, on an API basis. The conditions include, *inter alia*, dosage limitations, specific indications for use, required warnings, contraindications, and statements regarding drug-drug and drug-food interactions.[28] The cornerstone of the monograph system is regulation on the basis of the API and the dosage strength of that ingredient.[29] Within a given monograph category, the Agency allows certain APIs within a given dosage range and, often, combinations of the APIs. The monographs do not specify which inactive ingredients (*i.e.*, excipients) are permissible or impermissible--the drugs need only be safe and suitable for pharmaceutical use by patients without a physician's oversight. All the components must meet the applicable compendial standards, and the drug products must be manufactured in accordance with cGMPs.[30]

Thus, an OTC drug product: (1) whose API is covered by a monograph, *i.e.*, use "for a material time or to a material extent"; (2) is labeled in accordance with the applicable monograph, *i.e.*, adequate labeling; and (3) is formulated in accordance with compendial standards and manufactured in accordance with cGMPs, *i.e.*, equivalence, may be marketed in

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[25] FDC Act § 304.
[26] *See* 21 C.F.R. § 330.10, 37 Fed.Reg. 85 (Jan. 5, 1972), 37 Fed. Reg. 9464 (May 11, 1972).
[27] *Id.*
[28] *See, e.g.*, 21 C.F.R. Pt. 331 (Antacid Products for Over-the-Counter (OTC) Human Use).
[29] *See* 37 Fed. Reg. 9464 (May 11, 1972).
[30] See 21 C.F.R. § 330.1 (a) (referencing 21 C.F.R. Parts 210, 211, the cGMP regulations).

the U.S. without being the subject of an approved NDA or ANDA. These drugs are GRAS/E; therefore, no *in vivo* or *in vitro* bioavailability or bioequivalence data are required. No preclearance by FDA is required.

### C. Drug Listing Requirements

To complete our historical overview of FDA's regulation of prescription and OTC drugs, we address an important administrative requirement. The Drug Listing Act of 1972, 21 U.S.C. § 360, amended the FDC Act in order to provide FDA with knowledge and information about every drug marketed in the U.S.[31] It requires all drug establishments that are engaged in the manufacturing, preparation, propagation, compounding, or processing of a drug to register their establishments and list all of their commercially-marketed drug products with the Agency. The requirement applies to both prescription and OTC drug products. Drug products that are not properly listed are deemed to be misbranded and, therefore, subject to FDA enforcement action.[32] The Drug Listing Act also requires companies to update their listings twice annually.[33]

These statutory provisions were enacted to ensure that the manufacturers of all drug products in the United States, regardless of their legal basis for marketing, *e.g.*, new drug, GRAS/E, are known and on file with FDA.[34] In this way, the Agency has a complete list of all drug products on the market so that it can take prompt action against all such products containing the same API if safety issues arise. To further implement those statutory provisions and to ensure that marketers of all prescription drug products provide the Agency sufficient data on the safety of these marketed drug products, the Agency promulgated extensive rules mandating that marketers of all such drug products file adverse drug reaction reports, annual reports, etc.[35] In this way, the Agency can monitor the safe use of these drugs. In addition, through registration, FDA inspects the manufacturing of these drug products to ensure that they are produced in accord with compendial standards and cGMPs.

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[31] FDC Act § 510; 21 C.F.R. Pt. 207.
[32] FDC Act §§ 301 (p), 502(o).
[33] FDC Act § 510(j)(2); 21 C.F.R. § 207.21(b).
[34] S. Rep. No. 92-924 (1972), *as reprinted in* 1972 U.S.C.C.A.N. 2963, 2964.
[35] 21 C.F.R. § 310.305; 51 Fed. Reg. 24476 (July 3, 1986), 50 Fed. Reg. 11478 (March 21, 1985).

## D. Growth of the Generic Drug Industry Through the DESI Review, ANDAs, Issuance of the Orange Book, and Enactment of the Waxman-Hatch Act

### 1. Background

During this timeframe, the generic drug industry began to expand dramatically. This growth was attributable to a confluence of regulatory and legal developments in which FDA played a central role. These developments include the DESI Review process, the administrative creation of ANDAs, which permitted applications based on bioequivalence studies and chemistry, manufacturing, and controls ("CMC") data, the repeal of state antisubstitution laws,[36] and the increase in the costs of drug products to the states and the Department of Defense. All of FDA's and the states' regulatory policies were based on API regulation, and questions about drug substitution at the level of the final dosage form began to arise.

The status of the market is most clearly described in FDA's 1975 Notice of Enforcement Policy which stated that because DESI implementation was nearing completion, a clear policy for the future was warranted.[37] The notice was intended to accomplish three things. First, it announced FDA's interim enforcement policy that all DESI drugs could be marketed without being the subject of an NDA or ANDA if all remaining requirements laid out in the DESI notice for that product, as well as applicable bioavailability and bioequivalence standards, are met. Second, it provided that a drug that was not evaluated under the DESI review but covered by an NDA prior to October 10, 1962, would not require the submission of a subsequent NDA until FDA completed its own effectiveness evaluation or established an applicable bioequivalence requirement for the particular API. Finally, the notice proposed a codification of the enforcement policy to keep the public informed. This notice gave rise to the Orange Book (discussed *infra*).[38] In explaining the elimination of the ANDA requirement for drugs without bioequivalence concerns or special manufacturing problems, the 1975 Notice explained that "this form of control constitutes a more efficient allocation of [FDA's] resources by restricting the use of [ANDAs] to those drug products for which affirmative marketing approval is

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[36] *See* Drug Product Selection, Bureau of Consumer Protection Staff Report to the Federal Trade Commission (Dec. 1978) (providing a history of the spread of antisubstitution legislation).
[37] 40 Fed. Reg. 26142, 26146 (June 20, 1975).
[38] *Id.* at 26146.

necessary, while continuing to assure, through other means, the quality and labeling of those drug products which do not require such close control."[39]

The 1975 Notice of Enforcement Policy was immediately challenged on the grounds that FDA could not officially permit new drugs to be marketed without approved applications (NDAs or ANDAs), and it was withdrawn shortly thereafter in light of the court's order in *Hoffmann-La Roche, Inc. v. Weinberger.*[40] The Agency argued that it was implicit in the notice that a "me-too" drug could be marketed prior to NDA or ANDA approval, maintaining it would be inequitable to give a competitive advantage to companies with ISR drugs, marketed prior to a DESI notice, by allowing them to continue to market pending ANDA approval while keeping competing products off the market until ANDA approval. The court decided that FDA's policy of allowing a new drug to be marketed without approved NDAs contravened the 1962 Amendments and FDA's regulations.[41] In *Cutler v. Kennedy,*[42] FDA was again precluded from giving official status to unapproved new drugs (OTC drugs that were found not to be GRAS/E status).

These cases have precluded FDA from providing these products with any legal status or sanction as new drugs. These cases do NOT foreclose or inhibit FDA's authority to determine if a drug is GRAS/E or establish policies that implicitly do just that.[43]

### 2. The Orange Book

The Orange Book was created by FDA in the late 1970s in response to requests from several state health agencies to help implement their Medicaid drug purchase programs and the Department of Defense drug contracting programs to establish grounds for the safe and effective substitution of generic drugs for their pioneer counterparts,[44] *i.e.*, among drugs containing the same API. By this time, virtually every state had enacted laws or implemented regulations

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[39] *Id.*.
[40] *Hoffman-LaRoche, Inc. v. Weinberger,* (425 F. Supp. 890 (D.D.C. 1975). *See also* 40 Fed. Reg. 43531 (Sept. 22, 1975).
[41] 425 F. Supp. at 894 (citing 21 U.S.C. § 355; 21 C.F.R. §§ 314.1(a)(f), 314.012 (1974); *Am. Pub. Health Ass'n v. Veneman,* 349 F. Supp. 1311 (D.D.C. 1972) (other internal case references omitted).
[42] *Cutler v. Kennedy,* 475 F. Supp. 838 (D.D.C. 1979).
[43] *Public Citizen v. Bowen,* 833 F. 2d 364 (D.C. Cir. 1987).
[44] 45 Fed. Reg. 72582 (Oct. 31, 1980; 44 Fed. Reg. 2932 (Jan. 12, 1979).

encouraging the substitution of generic drug products on an API basis either according to a formulary (*i.e.*, positive formulary approach) or permitting substitution for all drugs except those specified (*i.e.*, negative formulary approach). The Agency, however, realized that it simply could not address the needs of every state individually.[45] Moreover, it was actually preferable to provide a single list based on a common set of criteria rather than apply varying definitions and criteria across the many states.[46] To accomplish this task, the Agency created the Approved List of Therapeutically Equivalent Drug Products, known as "The Orange Book."

The Orange Book created a unique rating system for therapeutic substitution of drug products containing the same API, and the system is applicable only to prescription drugs and drug products that have traversed the contemporary new drug approval system.

Two drugs are "therapeutically equivalent" if they are also pharmaceutically equivalent and are expected to bring the same safety profile and clinical effect when administered in accordance with the label.[47] Specifically, they are therapeutically equivalent if they meet the following criteria: "(1) they are approved as safe and effective; (2) they are pharmaceutical equivalents in that they (a) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity, and identity; (3) they are bioequivalent in that (a) they do not present a known or potential bioequivalence problem, and they meet an acceptable *in vitro* standard, or (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard; (4) they are adequately labeled; and (5) they are manufactured in compliance with [cGMPs]."[48] Nevertheless, they may differ in other characteristics, such as scoring, shape, mechanism of release, packaging, inactive ingredients, expiration period and, to a certain extent, labeling.[49]

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[45] Preface to 25th Ed., Orange Book at v.
[46] *Id.*
[47] Introduction, Preface to 25th Ed., Orange Book at viii.
[48] *Id.*
[49] *Id.*

To achieve therapeutic equivalence, an applicant for a generic drug product conducts bioequivalence studies, under 21 C.F.R. Part 320, which compare its drug product with the drug product that FDA determines to be the reference drug, normally the market leader for the API. The data showing bioequivalence can range from comparative *in vitro* dissolution tests to *in vivo* blood level studies comparing the drug products.[50] Moreover, FDA can waive the requirement for any test.[51] After reviewing the data, FDA approves the generic and issues a therapeutic equivalence code. If FDA concludes that the drug products are therapeutically equivalent, most states accept this decision, and if a prescription is written for a specific drug product, state substitution laws permit automatic substitution by a pharmacist of any therapeutically equivalent drug product without consultation or authorization of the physician.[52]

The enormous impact of the therapeutic equivalence decision is shown by the fact that FDA was sued to prevent the public release of the Orange Book.[53]

Enactment of the Drug Price Competition and Patent Term Restoration Act of 1984 ("Waxman-Hatch Act")[54] on September 24, 1984, served as a seminal date for the generic industry. The Waxman-Hatch Act created a mechanism for all drug products to enter the market generically through ANDAs,[55] and it also codified the Agency's above-described procedures and criteria for determining therapeutic equivalence, including the Agency's regulations for determining bioavailability and bioequivalence.[56]

The Orange Book process was also officially recognized.[57] Quite significantly, the statute also created new independent categories of intellectual property which only protect drug products from generic competition that have NDAs approved after 1984 with contemporary

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[50] 21 C.F.R. § 320.24.
[51] 21 C.F.R. § 320.22 (c), (d).
[52] *See* Drug Product Selection, Bureau of Consumer Protection Staff, Report to the Federal Trade Commission (Dec. 1978).
[53] *Pharm.Mfrs. Ass'n v. Weinberger*, 411 F. Supp. 576 (D.D.C. 1976).
[54] Pub. L. No. 98-417.
[55] *Id.* at § 101.
[56] *Id.*
[57] *Id.*

clinical data that FDA has reviewed and approved from generic competition.[58] This intellectual property is commonly referred to as "Waxman-Hatch exclusivity," and it is applicable only to this closed set of drug products that can enter the prescription drug market through the NDA process after 1984.

### E. Summary

Through Congressional directives, regulatory initiatives, and extensive scientific review, FDA has developed common standards and criteria for determining the inter-changeability of OTC, prescription, and GRAS/E drug products as well as their legal status for regulatory enforcement. In all of these cases, FDA applies the same basic criteria: (1) the same API with a long history of safe use; (2) the same basic dosage form; (3) similar but not necessarily identical labeling; (4) and compliance with compendial standards and manufacture in accordance with cGMPs. For those new drugs whose APIs do NOT have a long history of use, *i.e.*, that have been marketed under approved applications, FDA has required bioequivalence data, either *in vivo* or *in vitro*, which must be submitted for Agency review and approval. For those drugs that have a long history of use, *i.e.*, "for a material time or to a material extent," the equivalence is shown by self certification of *in vitro* dissolution to a monograph or a compendial standard without FDA review. Under the Agency's regulations, this data can be reviewed during its inspections of the facilities which are listed in accord with the Drug Listing Act. If safety issues arise, the Agency can take prompt action against the drugs in every category.

## II. FDA HAS PRIMARY JURISDICTION TO RESOLVE MATTERS WITHIN ITS UNIQUE EXPERTISE FOR HYOSCYAMINE DRUG PRODUCTS

The case law is long and well-established that FDA retains primary jurisdiction to make determinations about the legal status of drug products, whether they are regulated as new drugs or have achieved GRAS/E status.[59] The Agency possesses the unique know-how to resolve these

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[58] *Id.*

[59] *See Weinberger v. Bentex*, 412 U.S. 645 (1973); *Weinberger v. Hynson, Westcott and Dunning, Inc.*, 412 U.S. 609 (1973); *CIBA Corp. v. Weinberger*, 412 U.S. 640 (1973); *see also USV Pharmaceutical Corporation v. Weinberger*, 412 U.S. 655 (1973).

types of matters, particularly regarding those products, such as hyoscyamine, whose marketing status could be alleged to be unclear. The U.S. Supreme Court upheld FDA's primary jurisdiction to determine the legal status of drugs, and to determine the scientific criteria that are applicable to these standards in a 1973 trilogy of cases sustaining FDA's application of all DESI notices to "me-too" drugs under the FDC Act.[60] Those cases refine FDA's primacy in categorizing products under its jurisdictions, *i.e.,* drug or device,[61] drug or cosmetic.[62]

Congress also created the standards for FDA to regulate prescription drug labeling,[63] promotion,[64] and manufacture.[65] The Agency implemented these mandates with comprehensive regulatory programs, fulfilling the congressional intent that FDA completely occupy the areas.[66] These programs address every element of prescription drug development, manufacture, and promotion. The long-established case law upholding FDA's primacy in the interpretation of its regulations, Agency actions with respect to those regulations, and the interpretation of its statutes, policies and practices, confirms that it is FDA—not the courts—that possesses the primary jurisdiction to determine the underlying issues presented in this Citizen Petition.[67] A review of FDA's regulations shows the comprehensiveness of the regulatory programs. For example, the cGMP regulations not only cover every element of prescription drug production,[68] but the courts have supported FDA's position that the cGMP standards are continually evolving.[69] Further, failure to comply with the cGMP standards subjects the deviator to potential criminal sanctions.[70]

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[60] *Id.*
[61] *See, e.g., United States v. Article of Drug ... BactoUnidisk*, 394, U.S. 784 (1969).
[62] *See, e.g., United States v. Article...Sudden Change*, 409 F. 2d 734 (2d Cir. 1969).
[63] FDC Act § 502.
[64] FDA Act § 502(n).
[65] FDC Act § 501.
[66] 21 C.F.R. Parts 201, 202, 203.
[67] See *Weinberger v. Bentex*, 412 U.S. 645 (1973); *Weinberger v. Hynson, Westcott and Dunning, Inc.*, 412 U.S. 609 (1973); *CIBA Corp. v. Weinberger*, 412 U.S. 640 (1973); *see also USV Pharma. Corp. v. Weinberger*, 412 U.S. 655 (1973).
[68] 21 C.F.R. Parts 210, 211.
[69] *See, e.g., United States v. Barr Labs.*, 812 F. Supp. 458 (D.N.J. 1993).
[70] *See, e.g., United States v. Copanos*, 12-89 Food & Drug L. Reps. 26 (D. MD 1989); *United States v. Morton-Norwich Prods,. Inc.*, 461 F. Supp. 760 (N.D. N.Y. 1978).

Congress's intent for FDA to totally consume the area of the regulation of prescription drug labeling and promotion is shown not only by the Agency's long-established regulations and enforcement policies, but is also reinforced by recent Congressional pronouncements. In enacting the Food and Drug Administration Modernization Act ("FDAMA") in 1997,[71] Congress explicitly intended FDA to rigorously regulate the promotional materials for off-label uses of prescription drugs by establishing strict limits on the distribution of the information and the submission of the information to FDA for review.[72] Limitations on the dissemination of pharmacoeconomic information were also imposed in that statute.[73] Therefore, there is no question that Congress intended for FDA to occupy this authoritative space through comprehensive regulation derived through its unique experience and expertise. With these FDA powers and historic regulatory policies in mind, it is critical now to examine the marketplace as it applies to hyoscyamine drug products.

## III. USING ITS ENFORCEMENT DISCRETION IN THE DESI FINALIZATION, GRANDFATHER, AND PARAGRAPH XIV AREAS, FDA HAS CREATED GRAS/E CRITERIA FOR HYOSCYAMINE AND HYOSCYAMINE CONTAINING DRUG PRODUCTS

Under the rubric of nonreviewable enforcement discretion, FDA has found that organized regulatory action against the above cited categories of products has been unnecessary for decades. Despite enactment of the Drug Amendments of 1962 and the Waxman-Hatch Act in 1984, thousands of drug products have remained on the market, and many have entered the market in the last several decades under various of the above-cited legal theories that, to date, have not been substantiated. Moreover, the competitive practices have grown exponentially, with the manufacturers of these products becoming more aggressive in their assertions and actions.

FDA has the primary jurisdiction to act here when necessary, but it has seldom deemed it necessary to do so. Rather, it has used the holdings in *Hoffman-LaRoche v. Weinberger* and

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[71] Pub. L. No. 105-115 (Nov. 21, 1997).
[72] *Id.* at § 401
[73] Id. at § 114.

*Cutler v. Kennedy* to create enforcement priorities that may not be subject to judicial review under *Heckler v. Chaney.*[74] In *Heckler*, the Supreme Court held that the Agency's decision to refrain from exercising its enforcement powers often involves a complex balancing of many factors that are within the Agency's expertise, and that an Agency is better qualified than a court to address the multiple variables involved in the proper ordering of its priorities. For these reasons, after almost a half century of inaction, FDA has determined that these drugs are GRAS/E. Just as it has primary jurisdiction to determine new drug status, FDA has primary jurisdiction to determine GRAS/E. Through its actions and policies, as a matter of fact and law, FDA, in fact, has concluded that these products have been used "to a material extent or for a material time" and are GRAS/E.

As a practical matter, no products on the market bear labeling that has remained unchanged since 1938. The Agency and the courts have been unanimous in concluding that qualification for grandfather status from the premarket approval requirements of the FDC Act is an almost insurmountable hurdle.[75]

Accordingly, FDA has established a risk-based priority system for bringing this universe of drug products into compliance with the FDC Act ostensibly using its enforcement discretion as the basis under the *Hoffman-LaRoche, Inc. v. Weinberger, Cutler v. Kennedy* and *Heckler v. Chaney.* FDA's draft guidance on marketed unapproved drugs explains the Agency's more recent use of a risk-based enforcement approach, including efforts to identify drugs that are purported to be marketed illegally as new drugs, *i.e.*, drugs that are not GRAS/E without approved NDAs. The Agency is prioritizing review of these drugs according to their potential public health concerns.[76] This policy confirms that, in the face of decades-long inaction by FDA regarding these prescription drug products, there is an implicit recognition that the hundreds of thousands of prescriptions written each year by physicans, subsequently dispensed by registered pharmacists in accordance with state requirements, have become established professional

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[74] *Heckler v. Chaney,* 470 U.S. 821 (1985).
[75] *United States v. Allan Drug,* 357 F.2d 713 (10th Cir. 1966); *Rutherford v. United States,* 542 F.2d 1137 (10th Cir. 1976).
[76] *Marketed Unapproved Drugs -- Compliance Policy Guide* (Oct. 2003) ("2003 Draft Guidance"), at 2.

practices that are consistent with the public health. The objective of this petition is to urge and request the FDA to end the large disparity between legal theory and practical policy, as applied to this large category of drugs, by making explicit this recognition, in the form of publicly established FDA regulatory criteria for hyoscyamine drug products. In reality, this policy confirms FDA's *de facto* and *de jure* determination of GRAS/E status for these hyoscyamine drugs.

This approach has permitted the Agency to impose severe sanctions when safety issues have arisen or when the GRAS/E status of these drug products have been undermined or challenged in any other meaningful context. For example, in *Griffin v. O'Neal, Jones & Feldman, Inc.*, criminal sanctions were sought for injuries suffered from E-Ferol, an unapproved Vitamin E injection administered to a newborn infant.[77]

When manufacturing consistency, stability, and effectiveness issues have arisen, FDA has acted on an API basis, *e.g.*, levothyroxine. As FDA states in its press release and information page on the first approved levothyroxine product, Unithroid, levothyroxine products have been marketed in the U.S. since the 1950s.[78] "[The] products that have been on the market have been associated with stability and potency problems. These problems have resulted in product recalls and have the potential to cause serious health consequences to the public."[79]

Another example is guaifenesin controlled release products. When new dosage forms have sought exclusivity or uniqueness by seeking FDA review and approval of the data, it is addressed on an active ingredient basis. Adams Laboratories, Inc. sought prescription drug status for its controlled release guaifenesin product. FDA made a determination that the product

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[77] 604 F. Supp. 717 (Mar. 14, 1985) (dismissing the case because certain requirements were not met to establish criminal liability under the statute being applied).

[78] Unithroid information, CDER, http://www.fda.gov/cder/drug/infopage/unithroid/unithroid.htm; FDA Issues Guidance on Levothyroxine Sodium Products Compliance, FDA Talk Paper T01-28, July 12, 2001, <http://www.fda.gov/bbs/topics/ANSWERS/2001/ANS01089.html>.

[79] FDA approves First NDA for Levothyroxine Sodium, FDA Talk Paper T00-36, Augs. 22, 2000.

should be marketed OTC but agreed to initiate enforcement action against those controlled release guaifenesin products that were marketed without FDA approval.[80]

FDA's 2003 Draft Guidance, which supersedes CPG 7132c.02, applies to all new drugs subject to pre-market approval. The Guidance sets out the Agency's enforcement strategy, which shifts focus from reliance on DESI status (as stated in the prior CPG) to potential risk to public safety. The Agency will take action first against drugs with potential direct and indirect safety risks, then consider actions against those drugs considered ineffective or fraudulent. FDA expressly states that it will make these determinations and take subsequent actions on an active ingredient basis. As such, Agency action will be initiated against all products containing the "problem" active ingredient. Additionally, the Guidance states that FDA continues to have the discretion to decide, on a case-by-case basis, whether to allow a product to continue to be marketed temporarily, even after it is found to be on the market illegally.

In sum, FDA's policies recognize the *de facto* and *de jure* GRAS/E status for these drugs that has existed for decades. Unfortunately, statements in the Agency's brief filed in *Florida Breckenridge, Inc. v. Solvay Pharmaceuticals, Inc.*,[81] have led to misuse of FDA's position, unintended market consequences, and confusion in the marketplace. FDA's memorandum attempted to clarify the situation by stating that a showing of equivalence between drug products must be established in accordance with the requirements set forth in the applicable FDA regulations. This memorandum confirms that GRAS/E status can be achieved by relying on general criteria. Specifically, it states that "[a] mere showing of pharmaceutical or chemical equivalence is inadequate to demonstrate that the two drugs will be equally safe and effective because the difference in excipients may affect the bioavailability of a drug's active ingredients. The FDA has developed detailed regulatory requirements that set out the acceptable methods of demonstrating bioequivalence."[82] The regulations cited by FDA include several *in vivo* and *in vitro* methods. In FDA's words, "[t]he selection of the method used to meet an *in vivo* or *in vitro*

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[80] *See* Warning Letter to Allscripts Healthcare Solutions from FDA, CDER, Office of Compliance (Oct. 11, 2000); Warning Letter to Carolina Pharmaceuticals, Inc. from FDA, Atlanta District Director (March 12, 2004).
[81] *Florida Breckenridge, Inc. v. Solvay Pharm., Inc.*, 174 F.3d 1227 (11th Cir. 1999).
[82] Brief for the United States of America as Amicus Curiae at 19-20 ((No. 98-4606, July 1998) (citing *U.S. v. Generix Drug Corp.*, 460 U.S. 453, 455 (1983)); 21 C.F.R. §§ 320.1-320.63.

testing requirement depends upon the purpose of the study, the analytical methods available, and the nature of the drug product."[83] Specifically, this would include "[a] currently available in vitro test acceptable to FDA (usually a *dissolution rate test*) that ensures human *in vivo* bioavailability."[84] Waiver of the testing is also expressly permitted by the Agency's regulations in many cases. The lack of safety issues for these drugs has almost never required FDA action. Thus, for these GRAS/E products, these statements and criteria, including the waivers and *in vitro* dissolution tests, are standard and appropriate methods of establishing equivalence.

This safe marketplace has not required FDA regulatory action, and the lack of FDA action has recreated a quixotic marketplace that the Drug Amendments of 1962, the DESI Review, the Drug Listing Act, the OTC Drug Review, and the Waxman-Hatch Act were implemented to correct. As a result, some drug companies are exploiting this confusion by claiming uniqueness under the FDC Act, the right to market exclusivity and non-substitutability. Moreover, some pharmaceutical manufacturers are taking the position that matters involving cGMP compliance and the regulation of prescription drug advertising for hyoscyamine drug products are within the province of the federal district courts rather than for the Agency to determine. FDA's inaction has invited litigation on the very jurisdictional issues that the Agency fought for decades to establish. Therefore, for FDA to maintain its obligations to protect the public health, protect its jurisdiction and to ensure consistent public standards for regulation, FDA must establish criteria for the hyoscyamine GRAS/E drugs. Establishment of such criteria will confirm the therapeutic substitutability of these drugs without the need for additional data.

## IV. HYOSCYAMINE AND HYOSCYAMINE-CONTAINING DRUG PRODUCTS SATISFY FDA's *DE FACTO* GRAS/E CRITERIA.

### A. Background of Hyoscyamine and Hyoscyamine-containing prescription drug products.

A long history of safe hyoscyamine usage exists in its usage as an API in numerous drug products, including ISR products, establishing the use of hyoscyamine to a material time and

[83] 21 C.F.R. § 320.24(a).
[84] 21 C.F.R. § 320.24(b)(5) (emphasis added).

extent. The API and its salts, *e.g.*, sulfate, have been marketed for gastrointestinal use for almost a century. In fact, they have been in use since prior to enactment of the FDC Act in 1938 as shown by that fact that hyoscyamine is expressly mentioned in that statute. Hyoscyamine, as Levsin, now marketed by Schwarz Pharma, was initially marketed about 1955,[85] and Schwarz introduced a new oral tablet form in 2001.[86] Hyoscyamine was also a Paragraph XIV drug,[87] and hyoscyamine and hyoscyamine-containing prescription drug products are also on the Weiss list.[88] Hyoscyamine is also a component of belladonna alkaloids, which have a similar history of use. Belladonna alkaloids have been considered as part of the DESI Review, and FDA has addressed the status of these drugs in prior correspondence 25 years ago. Specifically, the DESI II list includes numerous belladonna products.

Hyoscyamine and hyoscyamine-containing drug products are subject to the adverse drug reaction ("ADR") reporting requirements, and they have an excellent history of safe use. This long history of safe oral prescription use further has established that there is no evidence of any bioequivalence concerns for products containing this drug; nor have any unique concerns ever been raised concerning cGMP compliance regarding manufacture of the drugs or products containing the API.

No clinical data for hyoscyamine have been reviewed and approved by FDA since enactment of the Waxman-Hatch Act. Therefore, no argument can be made that any such product is entitled to market exclusivity under the Waxman-Hatch Act.

### B. Application of the Criteria

With this background for hyoscyamine, it is valuable to review the basic criteria that have long been used by FDA as the real basis for determining the GRAS/E status of Category I OTC drugs, therapeutic equivalent determinations, and the risks associated with enforcement decisions for the DESI compliance program. The criteria constitute GRAS/E criteria, and application of

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[85] Schwarz Pharma Inc.'s First Amended Complaint and Demand for Jury Trial at 5, *Schwarz Pharma Inc. v. Breckenridge Pharm.*, No. 02-C-0918 (E.D. Wi. Sept. 8, 2003).
[86] *Id.*
[87] 40 Fed. Reg. 52644, 52647 (Nov. 11, 1975).
[88] Compliance Report for DESI-2, DRLS-DESI-2 1000 (printout dated Sept. 3, 1987).

these criteria to hyoscyamine prescription oral tablets shows that hyoscyamine oral prescription tablets are GRAS/E. The criteria are: (1) there is a long history of safe active ingredient usage as a prescription drug product; (2) the products are marketed in the same basic dosage form; (3) the labeling is essentially the same and, to the extent that there is minor variation, verbatim congruence is not required; and (4) they comport with the applicable compendial criteria and are manufactured in compliance with cGMPs.

### 1. Same Active Ingredient

The first criterion is a long history of safe active ingredient usage in many drug products, including ISR drug products, *i.e.*, use of the active ingredient "for a material time or to a material extent." As described, there is a long history of safe API usage in multiple hyoscyamine products, including ISR products, that establishes the use of this drug for the sufficient time and extent.

### 2. Same Dosage Form

Hyoscyamine drug products have never demonstrated manufacturing problems, and the drug's safety record is unassailable. FDA has regulated conventional oral prescription tablets alike, and the hyoscyamine products fall squarely within that general category. Thus, for hyoscyamine prescription tablets, the basic principles set forth in 21 C.F.R. §§ 320.22 (c) and (d) apply. These provisions establish that comparative bioavailability data are unnecessary; a waiver is appropriate. At worst, evidence of *in vitro* dissolution data, such as that required for compliance with the compendium or cGMPs, is sufficient.

### 3. Labeling is Essentially the Same

As we enter an era of managed care where payors are seeking to contain drug costs by encouraging not only generic substitution and therapeutic equivalence, we are also moving towards therapeutic interchange. Substitutability decisions are made on an API basis and based on evidence that transcends FDA's approval for a particular indication for use, *e.g.*, pharmacoeconomic evidence, which is really a reflection of cost, literature, and reference standards. Because the labeled indications have been generally applicable to all hyoscyamine

and ISR products, no uniqueness of claims exists, and all hyoscyamine drug products are permitted to contain the same basic provisions. The labeling for hyoscyamine products is adequate to permit substitution and interchange as GRAS/E.

### 4. Compliance With Compendial Standards and cGMPs

Drug products marketed in the U.S. must comport with all applicable compendial standards, as well as cGMPs. Both of these comprehensive and scientifically-based sets of standards consist of ranges and standards that are dynamic but sufficiently flexible to regulate all of the APIs and dosage forms that are subject to them.

#### a. Compliance with Compendial Standards

The U.S. Pharmacopoeia ("USP") is recognized in the FDC Act as a legal creator of purity, identity and quality standards for drugs. It is an independent, science-based organization that is recognized as the official compendium for drugs marketed in the U.S. In fact, the FDC Act specifically defines "drug" as "articles recognized in the official United States Pharmacopoeia, official Homeopathic Pharmacopoeia of the United States, or official National Formulary . . ."[89]

The USP sets comprehensive specifications for drugs set forth in individual ingredient-specific "monographs". A product that is claimed to be "USP" must meet the applicable "monograph" for that product, and is held out to the public and to FDA as meeting all of the applicable standards of identity and quality that the monograph includes. This is measured only by the applicable USP tests, including tests for impurity, tablet dissolution, assay methods, degradation profiles and long-term stability. The USP monographs include the following: drug name; definition; packaging, storage and labeling requirements; and series of tests, test procedures and test acceptance criteria to ensure that products "will have the stipulated strength, quality, and purity" that are set forth in the particular monograph.[90]

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[89] FDC Act § 201(g)(1)(A). Further, the Act defines "official compendium" as "the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, official National Formulary . . ." FDC Act § 201(j).

[90] USP-NF -- An Overview, U.S. Pharmacopeia , available at <http://www.usp.org/USPNF/>.

Failure to meet these standards, applying the USP tests, deems a drug to be adulterated and misbranded under the FDC Act[91], regardless of whether that drug is considered a "new drug" or has achieved GRAS/E status.[92] Specifically, under the Act, any drug that "purports to be or is represented as a drug the name of which is recognized in an official compendium, and its strength differs from, or its quality or purity falls below, the standards set forth in such compendium" is considered to be adulterated.[93] Any drug that "purports to be a drug the name of which is recognized in an official compendium [is considered misbranded], unless it is packaged and labeled as prescribed therein."[94] This could subject the manufacturer to sanctions.

FDA's CPG's recognize the legality and eminence of the compendial standards.[95] Since the inception of the use of generic drug products, prior to enactment of the Waxman Hatch Act, FDA has recognized that compliance with compendial standards is a critical component of therapeutic equivalence.[96] In the course of a routine or investigational inspection of drug companies that manufacture hyoscyamine prescription drug products, FDA will presumably assess compliance with the compendial criteria. Therefore, this criterion is consistent with the Orange Book therapeutic equivalence criteria, as well as the OTC Drug Review and FDA's current policy for hyoscyamine drugs. For these reasons, compliance with the applicable compendial standards fulfills its status as GRAS/E for hyoscyamine tablets.

The USP monograph for Hyoscyamine Sulfate Tablets includes specifications for identity, tablet disintegration, and uniformity of dosage units.[97] Hyoscyamine tablets that fully conform to the monograph can be held out as "USP", which means they are considered by FDA to be of the highest quality and purity for human use.

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[91] FDC Act § 501(b), 502(g).
[92] FDC Act §§ 501, 502.
[93] FDC Act § 501(b).
[94] FDC Act § 502(g).
[95] *See* "Adulteration of Drugs Under Section 501(b) and 501(c) of the Act. Direct Reference Seizure Authority for Adulterated Drugs Under Section 501(b) (CPG 7132a.03)", Compliance Policy Guides Manual, Sec. 420.100 (May 1, 1992); "Performance of Tests for Compendial Requirements on Compendial Products (CPG 7132.05)", Compliance Policy Guides Manual, Sec. 420.400 (Oct. 1, 1980).
[96] Therapeutically Equivalent Drugs, Availability of List, Proposal, 44 Fed. Reg. 2932, 2939 (Jan. 12, 1979).
[97] Hyoscyamine Sulfate Tablets USP monograph, USP 28-NF 23, 2nd supp. CD-ROM (2005).

These types of standards have been recognized by FDA for those OTC drugs that are subject to an OTC drug monograph. As discussed *supra*, OTC monograph drugs are regulated by FDA on an API basis. An OTC drug product whose formulation and labeling are squarely covered by an applicable monograph for that drug category may be marketed without going through the NDA or ANDA approval pathway if the conditions set forth in that monograph are met. This has been so since the inception of the OTC Drug Review over 30 years ago.

**b. Compliance with cGMPs**

A fundamental criterion for manufacturing a drug under the FDC Act is compliance with cGMPs. The courts have held that cGMPs establish ever evolving, comprehensive criteria for every aspect of manufacturing a drug product from API specifications to batch production to post-marketing stability, sampling, and testing.[98] The cGMPs are an extremely comprehensive set of methodologies and procedures that must be followed in the "manufacture, processing, packing, or holding of a drug to assure that such drug meets the requirements of the act as to safety, and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess."[99] These requirements are applicable to all drug products, both OTC and prescription.[100] They apply to drug products that are marketed under approved NDAs and ANDAs, and of equal importance, FDA has applied these criteria to all of the drugs and drug products that are marketed under claims of DESI, Paragraph XIV, or grandfather status.[101]

Drugs that fail to conform to cGMPs are considered to be adulterated under the FDC Act,[102] and the drug itself, "as well as the person who is responsible for the failure to comply, shall be subject to regulatory action."[103] Repeated and continuing cGMP violations may ultimately result not only in civil action but also criminal sanctions against the offending

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[98] 21 C.F.R. Parts 210, 211.
[99] 21 C.F.R. § 210.1(a).
[100] "cGMP Enforcement Policy-OTC vs. Rx Drugs (CPG 7132.10)", Compliance Policy Guides Manual, Sec. 450.100 (Apr. 1982).
[101] *See* 43 Fed. Reg. 45014 (Sept. 29, 1978); 41 Fed. Reg. 6878 (Feb. 13, 1976).
[102] FDC Act § 501(a)(2)(B).
[103] 21 C.F.R. § 210.1(b).

company. For these reasons, compliance with cGMPs is another critical but longstanding criterion for satisfaction of GRAS/E status. These comprehensive procedures not only occupy the field but are clearly intended by FDA to do so.[104] Therefore, the Agency's interpretation of how the standards apply and whether a company has met them preempts any judicial determination of criteria and application.

The criterion that cGMPs be followed has been specifically applied to all hyoscyamine drug products for decades. Hyoscyamine products have not been the subject of unique cGMP violations. As explained above, hyoscyamine products have been recalled, but only due to manufacturing/cGMP violations, and these violations have been unrelated to Agency concerns about the safety of hyoscyamine generally.[105] As noted above, akin to the biostudy waiver provisions in 21 C.F.R. § 320.22, the lack of unique cGMP problems is one important factor in establishing the lack of evidence of a bioequivalence problem.

## V. FDA MUST USE ITS PRIMARY JURISDICTION TO CLARIFY THE INAPPLICABILITY OF WAXMAN-HATCH EXCLUSIVITY TO HYOSCYAMINE DRUGS AND TO CLARIFY THE AVAILABILITY OF CLAIMS FOR SUBSTITUTION OF HYOSCYAMINE DRUG PRODUCTS THAT SATISFY THE *DE FACTO* GRAS/E CRITERIA.

Because no prescription hyoscyamine drug products marketed in accord with the Weiss List have applications approved after September 24, 1984, the intellectual property provisions of the Waxman-Hatch Act are inapplicable. There is no market exclusivity; there is no basis for claiming any listing in the Orange Book and thus no basis for claiming protection from substitution by drugs unless they have approved ANDAs. Yet, companies are attempting to hijack the Orange Book terminology and benefits, including "exclusivity" and "non-substitutability" through district court litigation for the benefit of their hyoscyamine drug

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[104] *See United States v. Barr Labs.*, 812 F. Supp. 458 (D.N.J. 1993); *United States v. Copanos*, 12-89 Food & Drug L. Reps. 26 (D. MD 1989).

[105] *See, e.g.*, FDA Enforcement Report 05-31 (Aug. 3, 2005) (Class II Recall of Hyoscyamine Sulfate Oral Solution, USP due to impurity discovered during routine long-term stability testing) available at <http://www.fda.gov/bbs/topics/enforce/2005/ENF00911.html >; FDA Enforcement Report 03-28 (July 9, 2003) (Class III Recall of Levsin Elixir (hyoscyamine sulfate elixir, USP) due to mislabeling) available at <http://www.fda.gov/bbs/topics/enforce/2003/ENF00803.html >).

products. It is legally unreasonable for the Agency to stand mute while companies, in federal court, assert Orange Book status and benefits about the legal status of their products that do not exist. In turn, this private litigation impedes companies from reaping the benefits of marketing prescription drug products that comport with the Agency's *de facto* standards of equivalence (*i.e.*, GRAS/E drugs). Clarity is necessary through the adoption of the criteria to fulfill FDA's obligation to protect the public and provide competitively priced pharmaceutical products that are equivalent. Absent clarity from FDA, companies whose products do not fit squarely into any clear regulatory scheme other than having GRAS/E status will be unjustifiably penalized.

For prescription drug products, FDA has primary jurisdiction to determine legal status (*e.g.*, prescription, OTC, new, GRAS/E). The Agency has primary jurisdiction to regulate all aspects of manufacturing and distribution, *e.g.*, compliance with compendial standards, cGMPs, as well as drug labeling and promotion. Congress has further inserted FDA into the regulation of information dissemination relating to prescription drug products by enacting legislation that restricts the unfettered ability to disseminate off-label information for prescription drug products as well as pharmacoeconomic data.

Claims of market exclusivity and nonsubstitutability fall squarely within FDA's jurisdiction as shown by its proposal to regulate information on therapeutic ratings in 1998. FDA has established criteria for assessing therapeutic equivalence of drug products that have approved NDAs and ANDAs. These criteria serve as the basis for recommendations to state boards of pharmacy, P&T committees, private insurers, and information services. For GRAS/E OTC drugs that self-certify, FDA has established analogous criteria that are used by these formulary-setting bodies when such decisions are necessary. For hyoscyamine and hyoscyamine-containing prescription drug products, FDA for decades established *de facto* criteria for determining equivalence, which are analogous to the criteria set for the other two categories. Public recognition of these or analogous standards is necessary to ensure that decisions that are being made every day are legally and scientifically correct and consistent with FDA's expertise. The pressures of implementation of Medicare Part D will only increase the demands on the Agency to make these decisions. If it does not act, not only will the private

sector act, but more litigation will follow that has the ability to throw the science and policy into a scientific and promotional maze. If that occurs, the Agency may never be able to regain its preeminence as the definitive legal and scientific standard for drug manufacture, advertising and equivalence.

## VI. CONCLUSION

Hyoscyamine and hyoscyamine-containing drug products have been marketed for a material time and extent under numerous legal theories. Debate is growing over the criteria for determining the therapeutic equivalence for these drug products. Claims of market exclusivity and nonsubstitutability are being raised at the state level and in federal district court. Criteria are necessary to address these issues. FDA has established *de facto* therapeutic equivalence criteria for these drug products, which are consistent with its criteria for all analogous drug product categories under the FDC Act. These criteria show that the hyoscyamine drug products are GRAS/E, and thus therapeutically equivalent, which permit substitution. Establishment of criteria for hyoscyamine and hyoscyamine-containing drug products is necessary for FDA to maintain its primary jurisdiction over the regulation of these drug products. Failure to establish such criteria can lead to private litigation and inconsistent legal standards. Inaction by FDA will undermine its primary jurisdiction to determine the following: (1) the legal status of these prescription drug hyoscyamine products; (2) the legal standards for making and asserting market exclusivity; (3) the scientific standards for marketing these products; (4) the labeling and advertising of these products; and (5) the scientific standards for recommending or permitting the substitution of these products.

## VII. ENVIRONMENTAL IMPACT

This petition qualifies for categorical exclusion under 21 C.F.R. § 25.30(a), therefore no environmental assessment is necessary.

## CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

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